RESEARCH PAPER

Development and Evaluation of Novel Olmesartan Cocrystals: A Strategy for Improving Aqueous Solubility and Dissolution Rate

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ABSTRACT

Objective: The present study aimed to enhance the solubility, dissolution rate and oral bioavailability of Olmesartan Medoxomil, a poorly water-soluble antihypertensive agent, through the development of pharmaceutical co-crystals using salicylic acid and benzoic acid as co-formers.

Methods: Co-crystals of Olmesartan were prepared in 1:1 and 1:2 molar ratios using dry grinding (DG), liquid-assisted grinding (LAG) and solvent evaporation (SE) methods. The prepared co-crystals were evaluated for saturation solubility, Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Scanning Electron Microscopy (SEM) and in-vitro dissolution study.

Results: All co-crystal formulations showed a significant improvement in solubility and dissolution compared to pure Olmesartan. Among them, the optimized formulation OC-S2-SE (Olmesartan : Salicylic acid, 1:2, solvent evaporation) exhibited the highest saturation solubility (0.092 ± 0.012 mg/mL) and drug release (97.86% in 60 minutes). FTIR and DSC confirmed co-crystal formation through characteristic peak shifts and the emergence of a new thermal event at 115.96 °C. SEM analysis revealed a distinct change in surface morphology with uniform and compact crystal aggregates. Batch OC-S2-SE (Olmesartan:Salicylic acid, 1:2) emerged as the optimized formulation, offering nearly four-fold improvement in drug release compared to pure drug.

Conclusion: Co-crystallization of Olmesartan with salicylic acid, especially via solvent evaporation, is a promising strategy to overcome its solubility and bioavailability limitations. The study validates the potential of pharmaceutical co-crystals to improve the therapeutic efficacy of poorly water-soluble drugs.

Keywords: Olmesartan, co-crystals, Salicylic acid, Benzoic acid, Solubility enhancement, Bioavailability, Solvent evaporation

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INTRODUCTION

Solubility is a key determinant of oral bioavailability for many pharmaceutical compounds, especially those classified under Biopharmaceutical Classification System (BCS) Class II, which exhibit low aqueous solubility but high membrane permeability.[1,2] Among these, Olmesartan Medoxomil, an angiotensin II receptor antagonist widely used in the treatment of hypertension, presents a significant formulation challenge due to its poor aqueous solubility, which limits its dissolution rate and consequently its bioavailability.[3] Improving the solubility of Olmesartan is therefore a critical goal to ensure rapid onset of action and enhanced therapeutic efficacy. Various approaches have been explored to overcome solubility-limited bioavailability, including particle size reduction, solid dispersions, complexation, and salt formation.[4,5] However, newer and more promising strategies such as co-crystallization technique have gained attention for being efficient, scalable and compatible with regulatory requirements. Pharmaceutical co-crystals, formed by non- covalent interactions between the drug and a co-former, offer a viable route to improve the physicochemical properties of active pharmaceutical ingredients without altering their pharmacological activity.[6] Co-formers such as benzoic acid and salicylic acid, recognized as Generally Recognized as Safe (GRAS), have shown potential in forming stable co-crystals with improved solubility and dissolution profiles.[7]

This study focuses on the design and evaluation of Olmesartan co-crystals using benzoic acid and salicylic acid, to investigate their impact on equilibrium solubility, dissolution rate and potential bioavailability enhancement. By integrating crystal engineering, the research aims to offer a robust approach for overcoming the solubility limitations of Olmesartan and improving its clinical performance.

Development And Evaluation Of Novel Olmesartan Cocrystals: A Strategy For Improving Aqueous Solubility And Dissolution Rate

MATERIALS AND METHODS

Material

Olmesartan was obtained as a gift sample from Umedica Ltd., Mumbai, India. All other chemicals and solvents used were of pharmaceutical and analytical grade.

Methods

Preparation of co-crystal of Olmesartan

The co-crystals of Olmesartan were prepared by using thee different technique as described below:

Dry Grinding Method

In this method, Olmesartan Medoxomil and the selected co-former (benzoic acid or salicylic acid) were weighed accurately in 1:1 and 1:2 molar ratios using an analytical balance. The drug and co-former were transferred to a clean and dry mortar and ground manually using a pestle for 30–45 minutes under ambient conditions. The grinding process was carried out without any solvent. The appearance of a new phase e.g., change in texture, stickiness, or color indicated potential co-crystal formation. The resulting ground mass was collected, transferred to a clean container, and stored in a desiccator until further characterization and solubility analysis [8].

Liquid-Assisted Grinding (LAG) Method

In the liquid-assisted grinding method, Olmesartan Medoxomil and co-former (benzoic acid or salicylic acid) were accurately weighed in 1:1 and 1:2 molar ratios and placed in a mortar. To facilitate better molecular interaction and partial dissolution, a few drops of ethanol were added to the mixture. The components were then ground manually with a pestle for 30 minutes. The presence of solvent acts as a catalytic medium, enhancing interaction between drug and co-former molecules. After grinding, the resulting solid was dried at room temperature to evaporate residual solvent, then stored in an airtight container or desiccator. The solid was then used for further characterization and solubility testing. [9]

Solvent Evaporation Method

For the solvent evaporation method, Olmesartan Medoxomil and the selected co-former were weighed in 1:1 and 1:2 molar ratios and dissolved in a minimum volume of common solvent ethanol sufficient to dissolve both components. The mixture was stirred magnetically at room temperature for 2–3 hours to ensure complete dissolution and interaction. The clear solution was then slowly evaporated in a controlled oven (at 40°C) until a solid mass formed. The dried solid was scraped off, powdered gently using a mortar and pestle, and stored in a desiccator until further use. [10]

Table 1: Compositions of Olmesartan Co-crystals Using Benzoic Acid and Salicylic Acid

Batch Code	Drug:Co-former Ratio	Co-former	Method
OC-B1-DG	1:1	Benzoic Acid	Dry Grinding
OC-B2-DG	1:2	Benzoic Acid	Dry Grinding
OC-S1-DG	1:1	Salicylic Acid	Dry Grinding
OC-S2-DG	1:2	Salicylic Acid	Dry Grinding
OC-B1-LAG	1:1	Benzoic Acid	Liquid-Assisted Grinding
OC-B2-LAG	1:2	Benzoic Acid	Liquid-Assisted Grinding
OC-S1-LAG	1:1	Salicylic Acid	Liquid-Assisted Grinding
OC-S2-LAG	1:2	Salicylic Acid	Liquid-Assisted Grinding
OC-B1-SE	1:1	Benzoic Acid	Solvent Evaporation
OC-B2-SE	1:2	Benzoic Acid	Solvent Evaporation
OC-S1-SE	1:1	Salicylic Acid	Solvent Evaporation
OC-S2-SE	1:2	Salicylic Acid	Solvent Evaporation

Characterization of Co-crystal of Olmesartan Saturation Solubility Study

The saturation solubility of the pure Olmesartan and formulated co-crystals were assessed in distilled water. An excessive amount of drug and co-crystals were introduced to a glass vial that held 10 millilitres of study fluid. After that, samples were agitated on a rotary shaker set at 25° C±2°C for 48 hours at a steady pace. A Whatman filter paper no. 1 was then used to filter the saturated solutions. Filtrates were spectrophotometrically measured and suitably diluted. [11,12]

Fourier Transform Infra-Red Spectroscopy (FTIR)

The Fourier Transform Infrared (FTIR) spectroscopy study was conducted to investigate possible molecular interactions and confirm the formation of co-crystals between Olmesartan and selected co-formers (benzoic acid and salicylic acid). Samples including the pure drug and the prepared co-crystals were analyzed. Each sample was finely ground with IR potassium bromide (KBr) in a ratio of approximately 1:100 (sample:KBr) using a mortar and pestle. The homogenized mixture was then

compressed into a thin, transparent pellet using a hydraulic press under a pressure of about 8–10 tons for 2–3 minutes. The prepared pellets were subjected to FTIR analysis using an FTIR spectrophotometer (Shimadzu) in thecanning range of 4000–400 cm^{-1}. The obtained spectra were analysed for the presence, absence, or shifting of characteristic peaks corresponding to key functional groups such as – NH, –COOH, –OH, and –C=O. These spectral variations were compared between the pure drug, co-formers and co-crystal formulations. Shifts in peak positions, broadening or disappearance of specific peaks, and the appearance of new bands were interpreted as indicative of intermolecular interactions such as hydrogen bonding, suggesting successful co-crystal formation.

Differential Scanning Calorimetry (DSC)

The Differential Scanning Calorimetry (DSC) study was performed to evaluate the thermal behaviour and confirm co-crystal formation between Olmesartan and selected co-formers. Approximately 3–5 mg of each sample pure drug and prepared co-crystals were accurately weighed and placed in a sealed aluminum pan. An empty sealed pan was used as the reference. The analysis was carried out using a DSC instrument (Mettler Toledo) under a nitrogen atmosphere to prevent oxidative degradation. The samples were heated at a constant rate of 10 °C/min over a temperature range of 30 °C to 300 °C. The resulting thermograms were examined for changes in melting endotherms, including shifts, disappearance, or the emergence of new peaks, which were used to confirm the formation of new crystalline phases and possible co-crystal formation. [13,14]

Scanning Electron Microscopy (SEM)

The surface morphology and shape of prepared co-crystals in comparison with pure drug were observed by using a scanning electron microscope. For SEM measurement, Olmesartan and selected co-crystal formulation were fixed at metal stubs using double-sided adhesive tape. Drying of those samples in a vacuum chamber is necessary, then sputter-coated with a gold layer of 10 nm thick and viewed under a high-resolution scanning electron microscope (Tescan, vega 2, Czech Republic) by using different magnifications. [15]

***In - Vitro* Drug Dissolution Study**

In vitro drug dissolution study for pure Olmesartan and co-crystals were determined using USP paddle apparatus by dispersed powder technique. USP II dissolution equipment with a paddle stirrer was utilized for the study. Study was performed in PBS pH 6.8 solution. Sample equivalent to 20 mg of Olmesartan was added to 900 ml dissolution medium at 37 ±0.5°C and stirred at 50 rpm (Electrolab). At predetermined intervals, samples of the 5 mL dissolving medium were removed and replaced with fresh samples of the same volume. The samples drug content was examined using an absorbance measurement at 257 nm. The mean of at least three determinations was used to calculate the drug release. [16,17]

RESULTS AND DISCUSSION

Saturation Solubility Study

The saturation solubility study of pure Olmesartan and its co-crystals were performed in distilled water to evaluate the enhancement of solubility through co-crystal formation using different co-formers (benzoic acid and salicylic acid), stoichiometric ratios (1:1 and 1:2), and preparation methods (dry grinding, liquid-assisted grinding and solvent evaporation).

Table 2: Saturation Solubility Study

Batch Code	Drug:Co-former Ratio	Solubility (mg/mL)
Pure Olmesartan	-	0.019±0.006
OC-B1-DG	1:1	0.031±0.002
OC-B2-DG	1:2	0.037±0.003
OC-S1-DG	1:1	0.034±0.002
OC-S2-DG	1:2	0.039±0.003
OC-B1-LAG	1:1	0.038±0.003
OC-B2-LAG	1:2	0.043±0.004
OC-S1-LAG	1:1	0.041±0.003
OC-S2-LAG	1:2	0.046±0.004
OC-B1-SE	1:1	0.060±0.004
OC-B2-SE	1:2	0.068±0.005
OC-S1-SE	1:1	0.079±0.007
OC-S2-SE	1:2	0.092±0.012

(Data are mean ± SD (n=3))

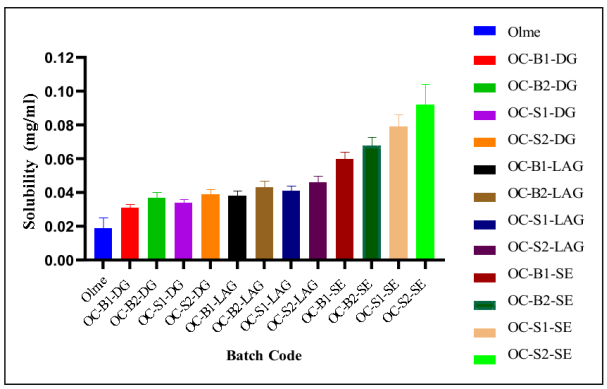

Figure 1: Saturation Solubility of Pure Olmesartan and Prepared Co-crystals in Distilled Water

The solubility of pure Olmesartan in distilled water was found to be 0.019 ± 0.006 mg/mL. The solubility of co-crystals prepared by the dry grinding method showed a moderate increase, with the 1:2 ratio of salicylic acid (OC-S2-DG) exhibiting the highest solubility among this group (0.039 ± 0.003 mg/mL), compared to 0.031–0.037 mg/mL for other dry- ground formulations. Co-crystals prepared using the liquid-assisted grinding (LAG) method demonstrated further enhancement in solubility. The OC-S2-LAG formulation (1:2 ratio with salicylic acid) showed a solubility of 0.046 ± 0.004 mg/mL, which was higher than the benzoic acid-based co-crystals (0.038–0.043 mg/mL).

The highest solubility values were observed in formulations prepared by the solvent evaporation method, with the 1:2 salicylic acid co-crystal (OC-S2-SE) showing a maximum solubility of 0.092 ± 0.012 mg/mL, which is approximately 4.84-fold higher than that of pure Olmesartan. Similarly, OC-S1-SE, OC-B2-SE, and OC-B1-SE showed significantly enhanced solubility values of 0.079 ± 0.007, 0.068 ± 0.005, and 0.060 ± 0.004 mg/mL, respectively.

The solubility data clearly indicate (Table 2) that co-crystallization significantly enhances the aqueous solubility of Olmesartan. Among all formulations, co-crystals prepared with salicylic acid showed consistently higher solubility than those prepared with benzoic acid, which may be attributed to the stronger hydrogen bonding and π–π interactions ofsalicylic acid with the Olmesartan molecule. Furthermore, increasing the co-former ratio from 1:1 to 1:2 generally resulted in greater solubility enhancement across all methods, suggesting a more efficient and complete interaction between drug and co-former at the higher molar ratio. Among the three methods employed, the solvent evaporation method proved to be the most effective in enhancing solubility, likely due to the better molecular arrangement and crystalline phase development during slow solvent removal, which facilitates stronger drug:co-former interactions. The OC-S2-SE batch (salicylic acid, 1:2, solvent evaporation) was found to be the most optimized formulation, providing a solubility increase of nearly five times compared to pure Olmesartan.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectrum of pure Olmesartan (Figure 2) exhibits characteristic peaks corresponding to its functional groups, confirming the structural integrity of the drug. Hydroxyl (–OH) stretching, broad peaks observed at 3700.83 cm^{-1}, 3628.64 cm^{-1}, and 3599.47 cm^{-1} indicate the presence of free –OH groups. Aromatic and aliphatic C–H stretching peaks was seen at 2976.34 cm^{-1} and 2887.41 cm^{-1}. Carbonyl (C=O) stretching: sharp peak at 1831.33 and 1705.72 cm^{-1} suggests the ester or acid functionalities present in Olmesartan. C=C stretching observed around 1476.06 cm^{-1}. C–N and C–O stretching was seen between 1300.10 and 1001.83 cm^{-1}.

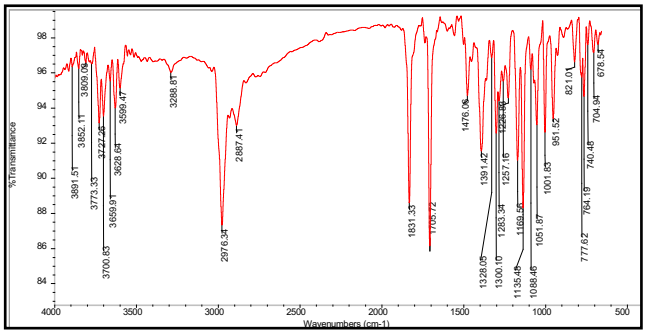

Figure 2: FTIR Spectra of Olmesartan

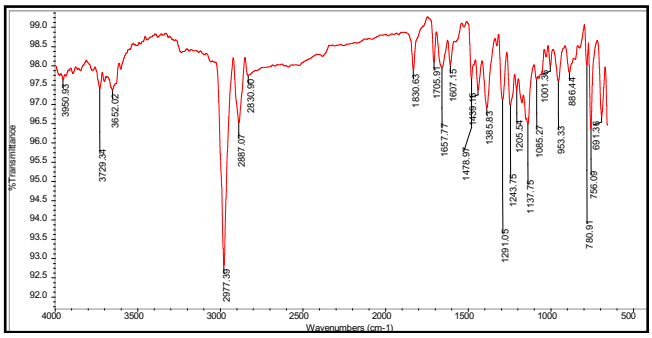

Figure 3: FTIR Spectra of Co-crystals of Olmesartan with Salicylic Acid

The FTIR spectrum of the co-crystals (Figure 3) prepared using Salicylic acid shows significant changes when compared to the pure drug. The broad –OH stretching bands around 3700–3500 cm^{-1} show reduced intensity and slight shifts (3729.34 cm^{-1}, 3662.02 cm^{-1}), indicating hydrogen bond formation between Olmesartan and Salicylic acid. The C=O stretching peak of Olmesartan at 1831.33 and 1705.72 cm^{-1} has shifted little and reduced peak intensity, suggesting interaction with the –OH group of Salicylic acid, forming hydrogen bonds. Changes in peaks in the aromatic region (1600–1450 cm^{-1}) also suggest π-π stacking or molecular interaction between aromatic rings of Olmesartan and Salicylic acid. The fingerprint region exhibits notable shifts and new peaks, further supporting structural changes due to co-crystal formation. The FTIR spectral analysis confirms the successful formation of Olmesartan–Salicylic acid co-crystals. The noticeable shifts and disappearance of key functional group peaks, particularly in the –OH and C=O regions, provide strong evidence of hydrogen bonding and non-covalent interactions between Olmesartan and Salicylic acid. These changes support the hypothesis of

new crystal lattice formation, distinct from the parent components, which is indicative of co-crystal formation.

Differential Scanning Calorimetry (DSC)

DSC Thermogram of Pure Olmesartan (Figure 4) exhibits a sharp endothermic peak with the onset temperature: 181.08 °C, peak temperature: 183.03 °C, endset temperature 187.16 °C and enthalpy (ΔH): -543.29 mJ. The sharp and singular endothermic peak corresponds to themelting point of pure Olmesartan, indicating its crystalline nature and high degree of purity. DSC Thermogram of Olmesartan–Salicylic Acid Co-crystals (OC-S2-SE) (Figure 5) displays two major endothermic events, first endothermic peak at 158.32°C corresponds to the melting of Salicylic acid, indicating its presence in the system and second endothermic peak at115.96 °C. This new, distinct peak is different from the melting point of pure Olmesartan (183.03 °C), suggesting the formation of a new crystalline phase, i.e., a co-crystal. Notably, the original melting point of Olmesartan is absent, confirming molecular interaction and new crystal lattice formation. The appearance of a new thermal event at a lower temperature (115.96 °C) supports the formation of a thermodynamically stable co-crystal structure. DSC study concluded that, the disappearance of Olmesartan's melting point and the presence of two distinct endothermic peaks (for co-former and new phase) strongly indicates successful co-crystal formation. These thermal transitions confirm molecular interaction and new solid- state phase formation, characteristic of co-crystals rather than simple physical mixtures.

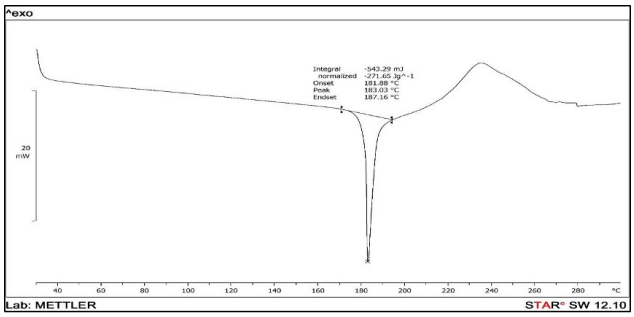

Figure 4: DSC Thermogram of Pure Olmesartan

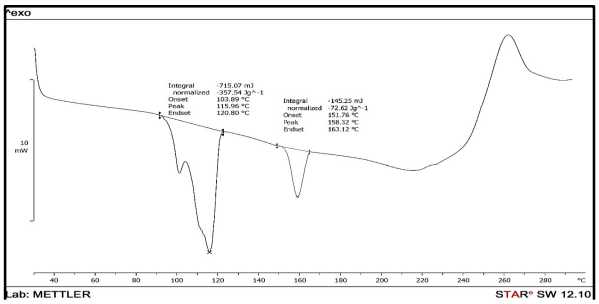

Figure 5: DSC Thermogram of Co-crystals of Olmesartan with Salicylic Acid (OC-S2- SE)

Scanning Electron Microscopy (SEM)

The surface morphology of pure Olmesartan and their co-crystal formulation was examined using Scanning Electron Microscopy (SEM).

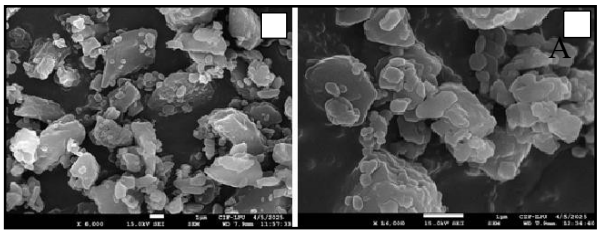

Figure 6: SEM Image of Pure Olmesartan (A) and SEM Image of Co-crystals of Olmesartan (B)

Pure Olmesartan exhibited irregular, non-uniform crystalline particles with rough and fragmented surfaces, indicating a less ordered crystalline structure (Figure 6A). The Olmesartan-salicylic acid co-crystals (Figure 6B) showed a distinct morphological transformation. The SEM images displayed aggregates of uniformly sized crystals, often arranged in a more compact and organized fashion. The co-crystals had a blocky and clusters appearance, suggesting strong molecular interactions and co-crystallization. The SEM analysis provided supportive evidence for successful co-crystal formation. The marked difference in morphology between the pure drug and the prepared co-crystals indicates the formation of a new solid phase. The aggregated crystalline structures observed in the co- crystals, absent in the pure drug, suggest molecular level interactions that promoted co-crystallization. The more uniform and compact aggregates may contribute to enhanced flow properties and potentially improved solubility and dissolution behaviour due to increased surface area and reduced crystallinity.

***In-Vitro* Dissolution Study**

The dissolution behaviour of pure Olmesartan and its various co-crystal formulations was evaluated in phosphate buffer pH 6.8 over a period of 60 minutes. The cumulative percentage drug release at specific time intervals (10, 20, 30, 40, 50, and 60 minutes) is presented in the figure 7. Pure Olmesartan showed a slow and limited dissolution, with only 24.51% drug release at 60 minutes. All co-crystal formulations demonstrated significantly enhanced dissolution compared to the pure drug. Among the dry grinding (DG) methods, OC-S2-DG (Olmesartan:Salicylic acid 1:2) showed the highest release of 71.39% at 60 min. Liquid- Assisted Grinding (LAG) further improved the dissolution. OC-S2-LAG

achieved 84.69% release and Solvent evaporation (SE) method yielded the best enhancement. The optimized formulation OC-S2-SE (Olmesartan:Salicylic acid 1:2) exhibited the highest drug release of 97.86% at 60 min, followed closely by OC-B2-SE and OC-S1-SE. The dissolution study reveals a significant improvement in the solubility and release rate of Olmesartan through co-crystal formation, particularly with salicylic acid as co-former and solvent evaporation as the method of preparation. Pure Olmesartan exhibited poor dissolution, likely due to its low aqueous solubility and crystalline nature, limiting its bioavailability. Co-crystallization using benzoic acid and salicylic acid in 1:1 and 1:2 molar ratios enhanced the dissolution profile. This can be attributed to, modification of crystal lattice energy, improved wettability and surface area and formation of a new multicomponent crystalline phase. Method of co-crystals preparation like, dry grinding improved dissolution to a moderate extent by facilitating weak intermolecular interactions. Liquid-assisted grinding (LAG) enhanced solvation and promoted better crystal integration of drug and co-former, while solvent evaporation (SE) showed superior performance as it promotes better molecular-level interaction and uniform co-crystal growth, resulting in faster and higher drug release. Salicylic acid proved to be a more effective co-former than benzoic acid, likely due to its stronger hydrogen bonding ability and acidic functional groups that interact favorably with Olmesartan. The 1:2 drug-to-coformer ratio consistently outperformed the 1:1 ratio, indicating that higher co-former content may facilitate more complete and stable co-crystal formation. Among all the formulations tested, OC-S2-SE (Olmesartan:Salicylic acid, 1:2, solvent evaporation) emerged as the optimized formulation, offering nearly four fold improvement in drug release compared to pure drug, thereby indicating potential for improved oral bioavailability.

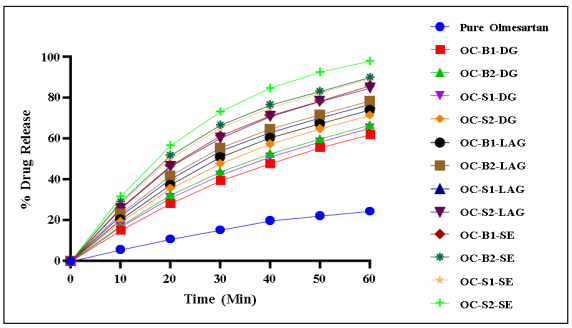

Figure 7: Dissolution profile of pure and Co-crystals of Olmesartan

CONCLUSION

The present study successfully demonstrated the potential of co-crystallization as a viable and effective strategy for enhancing the solubility, dissolution rate, and oral bioavailability of Olmesartan, a poorly water-soluble antihypertensive drug. Using salicylic acid and benzoic acid as co-formers in different molar ratios (1:1 and 1:2), co-crystals were prepared by dry grinding, liquid-assisted grinding (LAG), and solvent evaporation (SE) methods. Among these, the OC-S2-SE formulation (Olmesartan:Salicylic acid at 1:2 molar ratio, prepared by solvent evaporation emerged as the optimized formulation. Solubility of Olmesartan was significantly improved in all co-crystal formulations, with OC-S2-SE exhibiting a 4.84-fold increase compared to the pure drug. FTIR analysis confirmed successful co-crystal formation hydrogen bonding and non-covalent interactions between Olmesartan and the co-former. DSC thermograms further validated co-crystal formation, with the disappearance of the original melting point of Olmesartan and appearance of a new thermal event. The study conclusively shows that co-crystallization with salicylic acid using the solvent evaporation method not only enhances the physicochemical properties of Olmesartan but also significantly improves its in vitro performance. These findings support the broader application of pharmaceutical co-crystal technology as an efficient tool for overcoming solubility-limited bioavailability of BCS Class II drugs like Olmesartan.

CONFLICT OF INTEREST

No conflict of interest is declared.

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